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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,388	02/07/2001	Francis C. Szoka JR.	13054.01600	4514

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Nathan P. Koenig
Crosby, Heafey, Roach & May
P.O. Box 7936
San Francisco, CA 94120-7936

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/778,388	Applicant(s) SZOKA ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,13,15,16,19-21,24-36 and 38-52* is/are rejected.

7)☒ Claim(s) *10,14,17,18,22,23 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 5 on 5/3/02. Applicants elections without traverse of the species of PEG, distearoylglycerol, DOPE, hyaluronan, and glyme are acknowledged. After further consideration the restriction requirement is withdrawn. Claims 1-52 are pending and under consideration in this Office Action.

Applicant's assertion at page 1 of the response that methoxypolyethyleneglycol is not patentably distinct from polyethyleneglycol is noted. This is considered to be an admission that these species are obvious variants, and may be used in a rejection under 35 U.S.C. 103(a).

Claim Objections

Claims 22, 23, and 38-47 are objected to because they recite the acronym "POD" or the acronym "LOC". These acronyms are defined in the specification, but are not art-recognized terms. For this reason the first instance of each acronym in the claims should be presented parenthetically following the actual term the acronym represents. For example, in claim 22 "POD" should be replaced with "methoxypropylene glycol 2000-diortho esters-diastearoyl glycerol conjugate (POD)", and in claim 38, "LOC" should be replaced with "lipidic ortho ester conjugate (LOC)".

Claim 39 is objected to because it contains the text "Add support active lowering of pH" after the period.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38-41 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of delivering lipidic ortho ester conjugates comprising drugs or genes to cells, wherein the ortho ester is passively degraded by acidic pH in lysosomes, does not reasonably provide enablement for a method in which pH is lowered by an active step. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention embraces methods of delivering drugs or nucleic acids to cells through the use of lipidic ortho ester conjugates, in which hydrolysis of the ortho ester bond is increased with decreasing pH. The method recites an active step requiring a reduction in pH, however, the claims fail to recite in what compartment or solution the pH must be reduced, and the specification fails to teach how to perform this reduction inside a cell, or as required in claims 50-52, inside an animal. Clearly such a reduction in pH occurs in the endocytic pathway as endosomes mature into lysosomes, however this is a natural process which occurs without any active step. The specification fails to teach any active step for lowering the pH of a cell, or any particular site in an animal. While Applicant is not required to disclose that which is well known

in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of some region in which pH must be reduced, or some means of actively lowering the pH of a cell or of an animal cannot be considered minor details which can be omitted in the process of providing an enabling disclosure, and one of skill in the art could not practice the invention commensurate in scope with the claims without undue experimentation. This rejection can be overcome by eliminating the steps requiring reduction of pH.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 33, 38-47, 50-52 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 33 are indefinite because it is unclear what is encompassed by a "derivative" of a diketene or an acetal. The specification fails to provide a limiting definition of "derivative" in this context, so one of skill in the art cannot know the metes and bonds of the claims. For example, a single carbon atom could be considered to be a derivative of these groups because they both comprise carbon atoms.

Claims 38-47 are indefinite because it is unclear what is encompassed by the term "LOC". This term is not given a limiting definition in the specification, thus one of skill in the art cannot know the metes and bounds of the claims.

Claims 39 and 50-52 are indefinite because it is unclear what pH is to be reduced. Claim 39 requires "reducing pH", but does not recite what pH is to be reduced, i.e. it does not require pH reduction in any particular compartment or solution. Claims 50-52 recite "the pH" without antecedent basis, and similarly fail to describe what pH is to be reduced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-8, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Neville et al (US Patent 5,066,490, issued 11/19/91).

Neville teaches compositions comprising hydrophilic parts joined to hydrophobic parts by diortho ester linkers. For example, Neville teaches that monoclonal antibodies, which as globular proteins comprise both hydrophilic and hydrophobic parts, may be linked by a cleavable crosslinker to a toxin, which in turn may be linked by a cleavable crosslinker to a polyethylene glycol. See column 12, lines 61 and 62. The cleavable crosslinker may be a diortho ester. See e.g. column 6, lines 27-48. The polyethylene glycol may be methoxy polyethylene glycol of molecular weight 5000. See column 17, lines 5-11. The monoclonal antibody functions as a targeting ligand. The toxin may be either hydrophilic or hydrophobic or may comprise both hydrophilic and hydrophobic portions. For example, the toxin may be melphalan, which is a hydrophobic molecule. Alternatively the toxin may be daunomycin which is a hydrophilic molecule. Finally, the toxin may be a peptide toxin such as ricin, which contains both

hydrophilic and hydrophobic portions. Claim 12 is included in this rejection because a carbon atom may be considered to be a diketene acetal derivative, and the composition of Neville comprises a variety of carbon atoms.

Thus Neville anticipates the claims.

Claims 1, 2, 4, 11-13, 19, 30-33, 38, 39, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Sparer et al (US Patent 5,211,951, issued 5/18/93).

Sparer teaches compositions comprising bioerodable poly(ortho esters) and beneficial agents. The ortho esters may be 3,9-bis-(ethylidene)-2,4,8,10-tetraoxaspiro [5,5] undecane. See e.g. claim 9. The beneficial agent may be lipidic, e.g. estradiol. See column 2, line 54. The ortho esters may link the beneficial agents to polyethylene glycol. See column 7, lines 12-17. Pertinent to claim 19, the composition can be thought of as an encapsulator because it functions as an implant comprising the crosslinked PEG and beneficial agent. Pertinent to claims 38 and 39, the intended use of the composition is to deliver drugs to cells by implantation, followed by hydrolysis of the ortho ester linkers. See abstract, column 1, lines 50-60 and column 2, lines 3-5. Claims 30-33 are included in this rejection because the composition of Sparer appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the

prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

This Sawyer anticipates the claims.

Claims 1, 7-9, 19-21, 24-27, 30, 31, 34, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Pease et al (US Patent 4,891,3241, issued ½/90).

Pease teaches particles comprising luminescent molecules. The particles may be liposomes comprising the fusogenic lipid, DOPE. See column 6, lines 52-56; column 7, lines 27-49, especially line 47. The luminescent molecule may be hydrophilic, and may comprise a quaternary ammonium, e.g. rhodamine. See column 10, line 66. The luminescent molecule may be linked to the particle by an ortho ester. See column 12, lines 38-50. The composition of Pease comprises an encapsulator because liposomes may be considered encapsulators. The liposome may comprise a targeting moiety, e.g. a "specific binding partner" which may be a monoclonal antibody, a receptor antagonist, or a protein hormone. See column 3, lines 21-24; and column 8, lines 54-62; and column 15, lines 7-14. Claims 30, 31, 34, and 35 are included in this rejection because the composition of Pease appears to be substantially identical to that

claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Thus Pease anticipates the claims.

Claims 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Lishko et al (US Patent 5,753,263, issued 5/19/98).

Lishko teaches methods of delivering genes to animals by administering a composition comprising expression vectors encapsulated in liposomes. See column 43, lines 48-58. The liposomes may be pH-sensitive. See column 5, lines 16-18. While Lishko fails to teach an active step of decreasing pH, this step is inherent in the method because the pH-sensitive liposomes are taken up by the endocytic pathway and release the nucleic acids when endosomes

mature into lysosomes having acidic pH. Lishko also teaches that the liposome/DNA complexes may be lyophilized and rehydrated prior to use. See column 13, lines 33-38.

Thus Lishko anticipates the claims.

Claims 1, 2, 4, 6-9, 15, 19, 20, 24, 28, 29, 30-34, 36, 38, 39, 42 and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Schact et al (US Patent 6,312,727, issued 11/6/01).

Schact teaches cationic polymer-based carrier vehicles for the delivery of nucleic acids to target cells. See abstract. The hydrophilic cationic polymer may carry covalently bound polymers such as PEG, linked by pH-sensitive linkers such as ortho ester linkers. See column 3, line 60 to column 4, line 15; column 6, lines 27-33, and 49-58; and column 7, lines 52 and 53. Membrane-active lipids such as may be covalently linked to the polymer. See column 8, lines 53-59, and column 33, lines 15-20. Thus the composition of Schact comprises a hydrophilic cationic portion linked by an ortho ester linker to another portion comprising a hydrophobic region and PEG. The hydrophilic portion may comprise a targeting ligand such as a growth hormone, antibody or transferrin. See column 3, lines 14-36. The cationic polymer may comprise charged primary amines (polylysine), secondary amines/imidazoles (polyhistidine), tertiary amines, or quaternary ammoniums. See column 7, lines 9-26. Claims 19 and 20 are included because the composition can be considered to be an encapsulator. Claims 30-34 and 36 are included in this rejection because the composition of Schact appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to

that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Claims 33 and 36 are included in the rejection because it is unclear what is the scope of a "diketene acetal derivative". Such a derivative could be considered to be a carbon atom, and there are many carbon atoms in the composition of Schact. Claims 38 and 39 are included in the rejection because the compositions are intended to be delivered to cells and to compartments in which acid labile bonds are cleaved. See e.g. column 4, lines 10-15. Pertinent to claim 50, the compositions may be used to delivery nucleic acids to animals in vivo for the purpose of vaccination. See column 3, lines 6-10.

Thus Schact anticipates the claims.

Claims 1, 7, 8, 15, 16, 19-21, 24, 25, 30, 31, 34, 35, 38, 39, 42, and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Nantz et al et al (US Patent 6,200,599, issued 3/13/01).

Nantz teaches ortho ester lipids comprising a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo. See e.g. Fig. 1e; and column 14, lines 19-48. Claim 16 is included in the rejection because it is unclear what is the scope of a "dichloromethylmethyl ether derivative". Such a derivative could be considered to be a carbon atom, and there are many carbon atoms in the composition of Nantz. Claims 19 and 20 are included because the composition can be considered to be an encapsulator. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31. Claims 30, 31, 34, and 35 are included in this rejection because the composition of Nantz appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over either on of Sparer or Schact.

Sparer and Schact each teach compositions comprising a hydrophilic portion joined to a hydrophobic portion by an ortho ester linker, and in which the hydrophilic portion may comprise PEG. Neither of these references teaches methoxypolyethyleneglycol. However, the substitution of methoxypolyethyleneglycol for PEG in these inventions would be considered to be obvious to one of ordinary skill in the art, particularly in view of Applicants admission to this effect at page 1 of Paper No. 5.

Claims 41, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schact in view of Lishko.

Schact teaches liposomal encapsulators comprising ortho ester linkages and methods of administering them, but fails to teach any method for storing these compositions. Lishko teaches a method of storing lipidic compositions by lyophilizing them, and rehydrating them prior to use.

It would have been obvious to one of ordinary skill in the art at the time of the invention to lyophilize the compositions of Schact in order to store them, and to rehydrate them prior to use. One would have been motivated to do so because one of ordinary skill in the art appreciates that it is efficient to make large quantities of a composition which can be conveniently stored and used when needed. Given the teachings of Lishko one of ordinary skill in the art could have lyophilized and rehydrated the compositions of Schact with a reasonable expectation of success.

Thus the invention as a whole was *prima facie* obvious.

Claims 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pease in view of Lishko.

Pease teaches liposomal encapsulators comprising ortho ester linkages, but fails to teach any method for storing these compositions. Lishko teaches a method of storing lipidic compositions by lyophilizing them, and rehydrating them prior to use.

It would have been obvious to one of ordinary skill in the art at the time of the invention to lyophilize the compositions of Pease in order to store them, and to rehydrate them prior to use. One would have been motivated to do so because one of ordinary skill in the art appreciates that it is efficient to make large quantities of a composition which can be conveniently stored and used when needed. Given the teachings of Lishko one of ordinary skill in the art could have lyophilized and rehydrated the compositions of Pease with a reasonable expectation of success.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed. Claims 10, 14, 17, 18, 22, 23, and 37 are objected to because they depend from rejected base claims, but would be allowable if rewritten in independent form including all the limitations of the base claims, and if the objections raised above on pages 2 and 3 are addressed appropriately. Claims 10, 14, 17, 18, 22, 23, 37, 40, and 43-47 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

JAMES KETTER
PRIMARY EXAMINER

Richard Schnizer, Ph.D.